



VERIFICATION OF A TRANSLATION

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hereby declare that I am the translator of the document attached, Japanese
Patent Application No. 2002-244371, filed August 23, 2002, and certify that
the following is a true translation to the best of my knowledge and belief.

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【Name of the Invention】

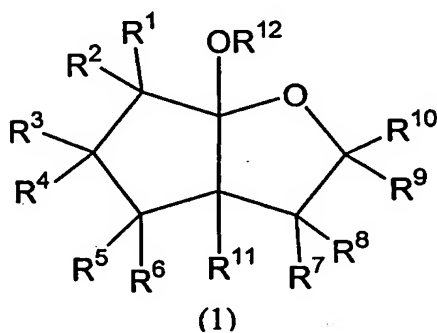
2-OXABICYCLO[3.3.0]OCTANE COMPOUNDS, PROCESS FOR
PRODUCING THE SAME, METHOD OF SEPARATING DIASTEREOMER
5 MIXTURE, AND METHOD OF OPTICALLY RESOLVING ALCOHOL

【Claims】

【Claim1】

A 2-oxabicyclo[3.3.0]octane compound of the following formula (1),

【chemical formula 1】



wherein R¹-R¹⁰ individually represent a hydrogen atom or a substituted or unsubstituted alkyl group having 1-20 carbon atoms, R¹¹ represents a substituted or unsubstituted alkenyl group, and R¹² represents a substituted or unsubstituted chiralic hydrocarbon group.

15 【Claim 2】

The compound according to claim 1, wherein R¹² is a substituted or unsubstituted chiralic secondary hydrocarbon group.

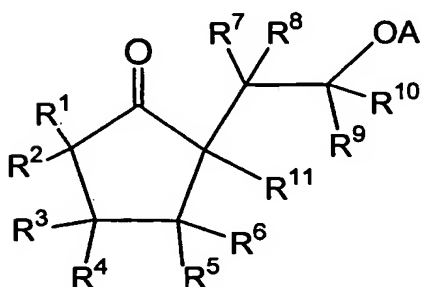
【Claim 3】

20 The compound according to claim 1, wherein R¹² is a chiralic secondary hydrocarbon group having a crosslinked structure or a chiralic secondary alkyl group substituted with an alkoxycarbonyl group.

【Claim 4】

A process for producing a 2-oxabicyclo[3.3.0]octane compound represented by the above formula (1) comprising reacting a compound of the formula (2),

【Chemical formula 2】



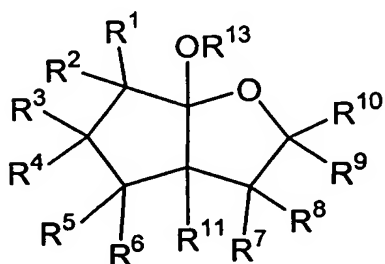
(2)

wherein the R^1 - R^{11} groups are the same as in the formula (1) and A is a hydrogen atom or a protective group for a hydroxyl group, with an optically active alcohol of the formula $R^{12}OH$, wherein R^{12} is the same as in the formula (1), in the presence of an acid catalyst.

【Claim 5】

A process for producing a 2-oxabicyclo[3.3.0]octane compound represented by the above formula (1) comprising reacting a 2-oxabicyclo[3.3.0]octane compound of the formula (3),

【Chemical formula 3】



(3)

wherein the R^1 - R^{11} groups are the same as in the formula (1) and R^{13} is a substituted or unsubstituted hydrocarbon group, with an alcohol of the formula $R^{12}OH$, wherein R^{12} is as defined above, in the presence of an acid catalyst.

【Claim 6】

A method for separating a diastereomer mixture of 2-oxabicyclo [3.3.0]octane compound of the above formula (1) comprising processing the diastereomer mixture of 2-oxabicyclo [3.3.0]octane compound of the above formula (1) using a simulated moving
5 bed chromatography to separate into individual diastereomers.

【Claim 7】

A method for separating a diastereomer mixture of 2-oxabicyclo [3.3.0]octane compound of the above formula (1) comprising distilling the diastereomer mixture of 2-oxabicyclo [3.3.0]octane compound of the above formula (1) to separate into individual
10 diastereomers.

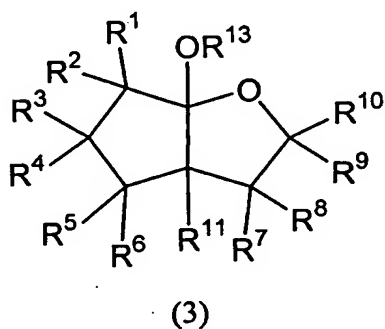
【Claim 8】

A method for optically resolving alcohol of the formula $R^{14}OH$, wherein R^{14} represents a substituted or unsubstituted hydrocarbon group having an asymmetric carbon atom, comprising,

15 a step of separating a diastereomer mixture of 2-oxabicyclo [3.3.0]octane compound of the above formula (1) described in any one of claims 1-3 into individual diastereomers,

a step of reacting the separated diastereomers with an alcohol of the formula $R^{13}OH$, wherein R^{13} is a substituted or unsubstituted hydrocarbon group, in the presence
20 of an acid catalyst to obtain a 2-oxabicyclo[3.3.0]octane compound of the formula (3),

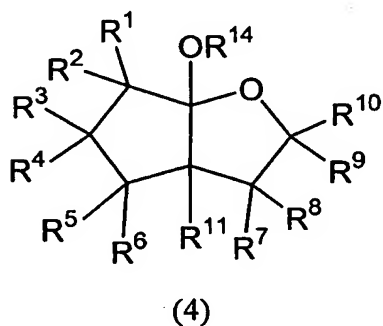
【Chemical formula 4】



wherein R^1 - R^{11} are the same as in the formula (1) and R^{13} is as defined above,

a step of reacting the compound of the formula (3) with an optical isomer mixture of alcohol of the formula $R^{14}OH$, wherein R^{14} is as defined above, in the presence of an acid catalyst to obtain a diastereomer mixture of the formula (4),

5 **【Chemical formula 5】**



wherein R^1 - R^{11} and R^{14} are the same as defined above,

a step of separating the resulting diastereomer mixture into individual diastereomers, and

10 a step of reacting the separated diastereomers with an alcohol of the formula $R^{15}OH$, wherein R^{15} represents a substituted or unsubstituted hydrocarbon group, in the presence of an acid catalyst to obtain an optically active alcohol of the formula $R^{14}OH$, wherein R^{14} is as defined above.

【Claim 9】

15 The method according to claim 8, wherein the step of separating the diastereomer mixture of the compound of the above formula (4) into individual diastereomers comprises processing the diastereomer mixture using simulated moving bed chromatography to separate into individual diastereomers.

【Claim 10】

20 The method according to claim 8, wherein the step of separating the diastereomer mixture of the compound of the above formula (4) into individual diastereomers comprises distilling the diastereomer mixture to separate into individual

diastereomers.

【Claim 11】

The method according to any one of claims 8-10, wherein the optical active alcohol of the formula $R^{14}OH$, wherein R^{14} is as defined above, and the compound of the above
5 formula (3) are isolated by reacting the separated diastereomer of the compound of the formula (4) with an alcohol of the formula $R^{13}OH$, wherein R^{13} is as defined above, in the presence of an acid catalyst, and the isolated compound of the formula (3) is reused as an optical resolution agent of alcohol.

【Detailed Description of the Invention】

10 **【0001】**

【Technical field to which the Invention pertains】

The present invention provides a 2-oxabicyclo[3.3.0]octane compound having a 2-oxabicyclo[3.3.0]octane ring with a chiral hydrocarbon group bonded to position 1 via an oxygen atom, a process for producing the compound, a method of separating a
15 diastereomer mixture of 2-oxabicyclo[3.3.0]octane compound, and a method of optically resolving alcohol.

【0002】

【Description of the Prior Art】

Many physiologically active substances such as pharmaceuticals, agricultural
20 chemicals, perfumes, and sweeteners are alcohols having an asymmetric carbon atom or compounds having a partial structure of such an alcohol (hereinafter referred to simply as "alcohols"). There may be optical isomers in such a compound. However, there may be a significant difference in the degree of physiological activity among these optical isomers. Some isomers exhibit physiological activity quite different from others. Therefore,
25 development of a method for separating an optical isomer mixture of alcohols easily without failure has been desired.

【0003】

As an example of optically resolving an alcohol, Synlett., (6), 862 (2000), J. Org. Chem., 64, 2638 (1999), and the like describe a method comprising allowing one of optical isomers to remain as the alcohol and transforming the other optical isomer into an ester derivative in a natural optically active environment (for example, internal organs of animals containing an esterified enzyme or hydrolyzed enzyme). However, since such an enzyme does not have chemical stability, in particular, thermal stability, the enzyme cannot be used under high temperature conditions. Further, it is difficult for the enzyme to be generally and widely accepted due to its high cost and difficulty in being procured in a large amount.

10 **【0004】**

Tetrahedron., Lett., 35, 4397 (1994) reported an experiment in which an ester prepared by condensing a carboxylic acid having an asymmetric carbon atom with an alcohol was separated into individual diastereomers by silica gel column chromatography. In principle, this is optical resolution of an alcohol.

15 However, since there are no general rules or principles for producing a highly separable diastereomer mixture, the method cannot be generally applied.

【0005】

And the mixture can rarely be separated into two optical isomers without being influenced by an external optically active factor, such as in the case of spontaneous resolution. General rules for separation do not exist. Accordingly, in almost all cases, it is highly difficult to speculate whether or not an optical isomer mixture of alcohol and the like can be separated into optically active compounds. The mixture is not easily separated in almost all cases.

【0006】

25 **【Problems to be solved by the invention】**

The present invention has been achieved in view of this situation and has an objective of providing a 2-oxabicyclo[3.3.0]octane compound which can be used as an

optical resolving agent of an optical isomer mixture of alcohol having an asymmetric carbon atom in the molecule, a process for producing such a compound, an optical resolving agent containing at least one 2-oxabicyclo[3.3.0]octane compound, a method of separating a diastereomer mixture, and a method of optically resolving alcohol using the optical resolving agent.

5 【0007】

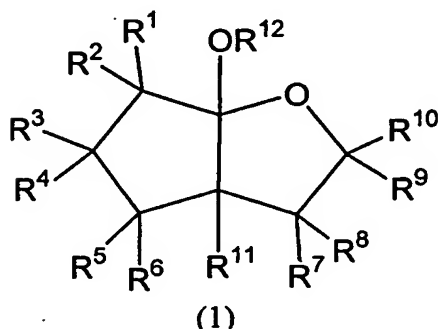
 【Means for Solving the Problem】

 The present inventors have found that (i) 1-alkoxy-2-oxabicyclo[3.3.0]octane compound with a substituted or unsubstituted chiral hydrocarbon group bonded to position 1 can be prepared efficiently by a reaction of a cyclopentanone compound having a 2-acetoxyethyl group and 2-propenyl group at position 2 of a cyclopentanone ring, with an optically active alcohol in the presence of an acid catalyst, and (ii) a diastereomer mixture of this compound can be efficiently separated into individual diastereomers by simulated moving bed chromatography or distillation, and (iii) an alcohol having an asymmetric carbon atom in the molecule can be optically resolved using the separated diastereomer. These findings led to the completion of the present invention.

 The present invention thus provides a 2-oxabicyclo [3.3.0]octane compound of the formula (1):

 【0008】

20 【Chemical formula 6】



 【0009】

wherein R^1 - R^{10} individually represent a hydrogen atom or a substituted or unsubstituted alkyl group having 1-20 carbon atoms, R^{11} represents a substituted or unsubstituted alkenyl group, and R^{12} represents a substituted or unsubstituted chiralic hydrocarbon group.

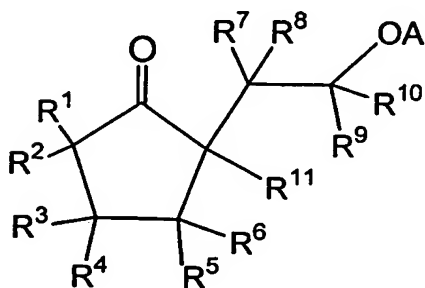
5 **【0010】**

In the 2-oxabicyclo[3.3.0]octane compound of the present invention, the R^{12} group is preferably a chiralic secondary hydrocarbon group which may have a substituent, and more preferably a chiralic secondary hydrocarbon group having a crosslinked structure or a chiralic secondary alkyl group substituted with an alkoxycarbonyl group.

10 The present invention further provides a process for producing a 2-oxabicyclo[3.3.0]octane compound represented by the above formula (1) comprising reacting a compound of the formula (2),

【0011】

【Chemical formula 7】



(2)

【0012】

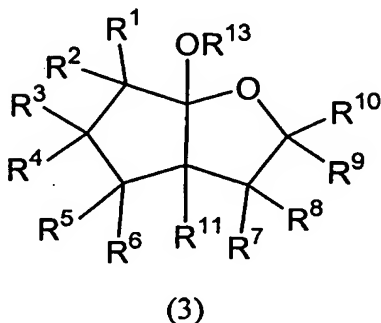
wherein the R^1 - R^{11} groups are the same as in the formula (1) and A represents a hydrogen atom or a protective group for a hydroxyl group, with an optically active alcohol of the formula $R^{12}OH$, wherein R^{12} is the same as in the formula (1), in the presence of an acid catalyst.

The present invention further provides a process for producing a 2-oxabicyclo[3.3.0]octane compound represented by the above formula (1) comprising

reacting a 2-oxabicyclo[3.3.0]octane compound of the formula (3),

【0013】

【Chemical formula 8】



5 【0014】

wherein the R^1 - R^{11} groups are the same as in the formula (1) and R^{13} is a substituted or unsubstituted hydrocarbon group, with an alcohol of the formula $R^{12}OH$, wherein R^{12} is as defined above, in the presence of an acid catalyst.

【0015】

10 The present invention further provides a method for separating a diastereomer mixture of 2-oxabicyclo [3.3.0]octane compound of the above formula (1) comprising processing the diastereomer mixture of 2-oxabicyclo [3.3.0]octane compound of the above formula (1) using a simulated moving bed chromatography to separate into individual diastereomers or distilling the diastereomer mixture to separate into individual
15 diastereomers.

【0016】

The present invention further provides a method of optically resolving alcohol of the formula $R^{14}OH$, wherein R^{14} represents a substituted or unsubstituted hydrocarbon group having an asymmetric carbon atom, comprising,

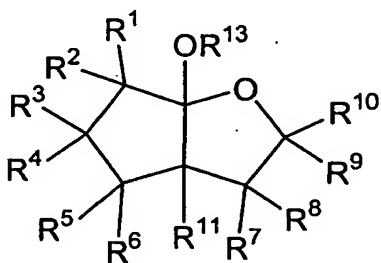
20 a step of separating a diastereomer mixture of 2-oxabicyclo [3.3.0]octane compound of the above formula (1) into individual diastereomers,

a step of reacting the separated diastereomers with an alcohol of the formula

$R^{13}OH$, wherein R^{13} is a substituted or unsubstituted hydrocarbon group, in the presence of an acid catalyst to obtain a 2-oxabicyclo[3.3.0]octane compound of the formula (3),

【0017】

【Chemical formula 9】



(3)

【0018】

wherein R^1 - R^{11} are the same as in the formula (1) and R^{13} is as defined above,

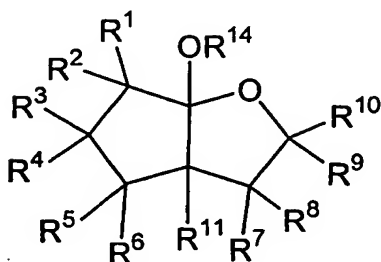
a step of reacting the compound of the formula (3) with an optical isomer

mixture of alcohol of the formula $R^{14}OH$, wherein R^{14} is as defined above, in the presence

of an acid catalyst to obtain a diastereomer mixture of the formula (4),

【0019】

【chemical formula 10】



(4)

【0020】

wherein R^1 - R^{11} and R^{14} are the same as defined above,

a step of separating the resulting diastereomer mixture into individual

diastereomers, and

a step of reacting the separated diastereomers with an alcohol of the formula, $R^{15}OH$, wherein R^{15} represents a substituted or unsubstituted hydrocarbon group, in the presence of an acid catalyst to obtain an optically active alcohol of the formula $R^{14}OH$, wherein R^{14} is as defined above.

5 **【0021】**

In the optical resolution method of alcohol in the present invention, the step of separating the diastereomer mixture of the compound of the above formula (4) into individual diastereomers preferably comprises processing the diastereomer mixture using a simulated moving bed chromatography to separate into individual diastereomers or
10 distilling the diastereomer mixture to separate into individual diastereomers.

【0022】

In the optical resolution method of alcohol of the present invention, it is preferable to isolate the compound of the above formula (3) from the optical active alcohol of the formula $R^{14}OH$, wherein R^{14} is as defined above, by reacting the separated
15 diastereomer of the compound of the formula (4) with an alcohol of the formula $R^{13}OH$, wherein R^{13} is as defined above, in the presence of an acid catalyst, and to reuse the isolated compound of the formula (3) as an optical resolution agent of alcohol.

【0023】

【Preferred Embodiment of the Invention】

20 The present invention will be described in detail in the following sections: (1) 2-oxabicyclo[3.3.0]octane compound, (2) process for producing 2-oxabicyclo[3.3.0]octane compound, (3) method for separating a diastereomer mixture of 2-oxabicyclo[3.3.0]octane compound, and (4) optical resolution method of alcohol.

【0024】

25 (1) 2-oxabicyclo[3.3.0]octane compound of the formula (1)

In the first place, the present invention provides a 2-oxabicyclo [3.3.0]octane compound of the above formula (1) (2-oxabicyclo [3.3.0]octane compound(1)).

【0025】

In the above formula, R^1 - R^{10} individually represent a hydrogen atom or a substituted or unsubstituted alkyl group having 1-20 carbon atoms.

Examples of the alkyl group having 1-20 carbon atoms include a methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, sec-butyl group, isobutyl group, n-pentyl group, n-hexyl group, n-octyl group, n-nonyl group, and n-decyl group. Examples of the substituent for these groups include a hydroxyl group; alkoxy groups such as a methoxy group and ethoxy group; alkylthio groups such as a methylthio group and ethylthio group; halogen atoms such as a fluorine atom and chlorine atom; and substituted or unsubstituted phenyl groups such as a phenyl group, 2-chlorophenyl group, 3-methoxyphenyl group, and 4-methylphenyl group. Of these, a compound in which R^1 - R^{10} are individually a hydrogen atom or a methyl group is preferable, since the compound can be easily made available or produced. A compound in which all R^1 - R^{10} groups are a hydrogen atom is particularly preferable.

15 【0026】

R^{11} represents a substituted or unsubstituted alkenyl group.

As examples of the alkenyl group, a vinyl group, 1-propenyl group, 2-propenyl group, isopropenyl group, 1-butenyl group, 2-butenyl group, 3-butenyl group, methallyl group, 1-pentenyl group, 2-pentenyl group, 3-pentenyl group, 1-hexenyl group, 2-hexenyl group, 3-hexenyl group, 1-heptenyl group, 2-heptenyl group, 5-heptenyl group, 1-octenyl group, 3-octenyl group, and 5-octenyl group can be given.

【0027】

There are no specific limitations to the substituents on the alkenyl group inasmuch as the compound is stable against an acid catalyst. As examples, a haloalkyl group, cycloalkyl group, alkoxy group, alkoxycarbonyl group, alkylthio group, alkylsulfonyl group, acyl group, nitro group, cyano group, hydroxyl group, halogen atom, substituted or unsubstituted phenyl group, and substituted or unsubstituted heterocyclic

group can be given. There are no specific limitations to the positions of these substituents. Two or more substituents, either the same or different, may bond to one group.

【0028】

As examples of the substituted or unsubstituted alkenyl group, an alkenyl group
5 such as a vinyl group, 1-propenyl group, 2-propenyl group, isopropenyl group, 1-butenyl group, 2-butenyl group, 3-butenyl group, methallyl group, 1-pentenyl group, 2-pentenyl group, and 2-ethyl-2-butenyl group; cinnamyl group, 4-chlorocinnamyl group, and 2-methylcinnamyl group can be given.

Of these, for the reasons of easy availability and easy manufacturing, R^{11} is
10 preferably a substituted or unsubstituted alkenyl group having 2-6 carbon atoms, more preferably an alkenyl group having 2-6 carbon atoms, and particularly preferably a 2-propenyl group.

【0029】

R^{12} represents a substituted or unsubstituted chiral hydrocarbon group,
15 specifically, R^{12} is a chiral group having at least one asymmetric carbon atom. When R^{12} is a group having an asymmetric carbon atom, the number of the asymmetric carbon atoms may be either one or two or more, and there are no specific limitations to the positions of the asymmetric carbon atoms.

【0030】

20 There are no specific limitations to the hydrocarbon group inasmuch as the hydrocarbon group is chiral (optical active), the hydrocarbon group may be a primary, secondary, or tertiary hydrocarbon group, preferably secondary hydrocarbon group. And although there are no specific limitations to number of carbon atoms in the hydrocarbon group, the number is normally 1 to 20, preferably 1 to 15.

25 **【0031】**

As the hydrocarbon group, an alkyl group, alkenyl group, alkynyl group, cycloalkyl group, cycloalkenyl group, aryl group, and hydrocarbon group having a

bridged structure (a structure in which two points not adjoining each other in a cyclic structure are bridged via one or more atoms) can be given.

【0032】

There are no specific limitation to the substituent for the hydrocarbon group
5 inasmuch as the substituents are stable in the acid. As examples, alkoxy group, alkoxy carbonyl group, alkylthio group, alkylsulfonyl group, acyl group, acylamino group, nitro group, cyano group, halogen atom, substituted or unsubstituted phenyl group, and substituted or unsubstituted heterocyclic group can be given. As examples of the substituent for the phenyl group or the heterocyclic group, halogen atoms such as fluorine
10 and chlorine; alkyl groups such as a methyl group and ethyl group; alkoxy groups such as a methoxy group and ethoxy group; a cyano group; and a nitro group can be given. There are no specific limitations to the positions of these substituents. Two or more substituents, either the same or different, may bond to the hydrocarbon group.

【0033】

15 Of these, R¹² is preferably a substituted or unsubstituted chiral secondary hydrocarbon group, more preferably a chiral secondary hydrocarbon group having a bridged structure or a chiral secondary alkyl group substituted with an alkoxy carbonyl group, particularly preferably a chiral 2-isopropyl-5-methyl-cyclohexyl group (menthyl group), a chiral 1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl group (bornyl group), and chiral
20 1-ethoxycarbonyl ethyl group, a chiral 1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl group (bornyl group) or a chiral 1-ethoxycarbonyl ethyl group.

【0034】

Specific examples of the 2-oxabicyclo[3.3.0]octane compound represented by the formula (1) include: 1-(d)-bornyloxy-5-(2-propenyl)-2-oxabicyclo[3.3.0]octane,
25 1-(1)-bornyloxy-5-(2-propenyl)-2-oxabicyclo[3.3.0]octane,
1-(1-(S))-ethoxycarbonyl ethoxy-5-(2-propenyl)-2-oxabicyclo[3.3.0]octane,
1-(1-(R))-ethoxycarbonyl ethoxy-5-(2-propenyl)-2-oxabicyclo[3.3.0]octane,

1-(1)-mentyloxy-5-(2-propenyl)-2-oxabicyclo[3.3.0]octane, and

1-(d)-mentyloxy-5-(2-propenyl)-2-oxabicyclo[3.3.0]octane.

【0035】

1-(d)-bornyloxy-5-(diphenylmethyl)-2-oxabicyclo[3.3.0]octane,

5 1-(1)-bornyloxy-5-(diphenylmethyl)-2-oxabicyclo[3.3.0]octane,

1-(1-(S)-ethoxycarbonyl)ethoxy-5-(diphenylmethyl)-2-oxabicyclo[3.3.0]octane,

1-(1-(R)-ethoxycarbonyl)ethoxy-5-(diphenylmethyl)-2-oxabicyclo[3.3.0]octane,

1-(1)-mentyloxy-5-(diphenylmethyl)-2-oxabicyclo[3.3.0]octane, and

1-(d)-mentyloxy-5-(diphenylmethyl)-2-oxabicyclo[3.3.0]octane.

10 【0036】

(2) Process for producing 2-oxabicyclo[3.3.0]octane compound (1)

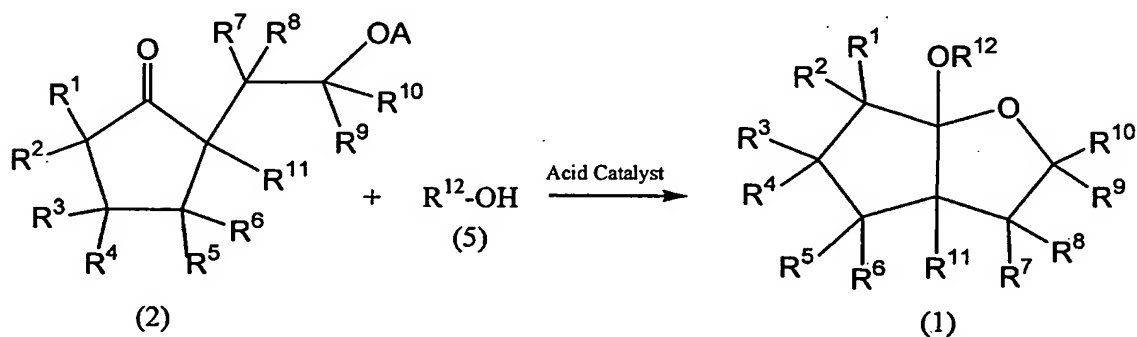
In the second place, the present invention provides a process for producing 2-oxabicyclo[3.3.0]octane compound (1).

15 The 2-oxabicyclo[3.3.0]octane compound (1) can be produced by the following process (1) or process (2).

(i) Process (1)

【0037】

【Chemical formula 11】



20 【0038】

The 2-oxabicyclo[3.3.0]octane compound (1) can be prepared by reacting a cyclopentanone compound of the formula (2) (hereinafter referred to as “cyclopentanone

compound (2)”) with an alcohol of the formula $R^{12}OH$ (hereinafter referred to as “alcohol (5)”) in the presence of an acid catalyst. The target compound can be directly obtained from the cyclopentanone compound (2) by this process.

【0039】

5 Although there are no specific limitations to the alcohol (5) inasmuch as the alcohol (5) is optically active, the alcohol may be a primary, secondary, or tertiary alcohol, a secondary alcohol is preferable, a secondary alcohol having 3-20 carbon atoms is more preferable due to easy availability and the capability of producing the target compound at a high yield.

10 【0040】

 As specific examples of the optically active secondary alcohol having 3-20 carbon atoms, menthols such as an optically active 2-isopropyl-5-methyl-cyclohexanol; lactic acid esters such as an optically active methyl lactate and optically active ethyl lactate; borneols such as an optically active 1-endo-borneol; synthetic perfumes such as
15 isocamphylcyclohexanol; and the like can be given.

 【0041】

 Of these, (d)-menthol, (l)-menthol, (d)-borneol, (l)-borneol, (S)-ethyl lactate, and (R)-ethyl lactate are preferable due to their easy availability, with (d)-borneol, (l)-borneol, (S)-ethyl lactate, and (R)-ethyl lactate being particularly preferable.

20 【0042】

 Although there are no specific limitations to the amount of the alcohol (5), the alcohol (5) is usually used in an amount of 1-100 mols, and preferably 1-5 mols, for 1 mol of the cyclopentanone compound (2).

 【0043】

25 The reaction can be carried out by stirring a mixture of the cyclopentanone compound (2) and the alcohol (5) in a suitable solvent or without using a solvent in the presence of an acid catalyst. As the acid catalyst, either a liquid acid catalyst or a solid

acid catalyst can be used without any specific limitations. For example, pyridinium p-toluenesulfonate (PPTS), p-toluenesulfonic acid (p-TsOH), montmorillonite, an acidic ion exchange resin, and synthetic zeolite (e.g. molecular sieve) can be given.

5 The acid catalyst is usually used in the amount of usually 0.0001-2 parts by weight, and preferably 0.001-1 part by weight, for 1 part by weight of the cyclopentanone compound (2).

【0044】

The reaction can be carried out either without using a solvent or using an inert solvent.

10 There are no specific limitations to the solvent used for the reaction inasmuch as the solvent is nonprotonic. Examples of the solvent include aromatic hydrocarbons such as benzene, toluene, xylene, and chlorobenzene; aliphatic hydrocarbons such as n-pentane, n-hexane, n-heptane, n-octane, cyclohexane, methylcyclohexane, and petroleum ether; esters such as ethyl acetate, propyl acetate, and butyl acetate;
15 halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, and 1,2-dichloroethane; ethers such as diethyl ether, dibutyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane, cyclopentyl methyl ether, and anisole; and amides such as N,N-dimethylformamide, N,N-dimethylacetamide, and N-methylpyrrolidone. These solvents may be used either individually or in combination of two or more. Of
20 these, an organic solvents having a comparatively low boiling point such as aromatic hydrocarbons, aliphatic hydrocarbons, and halogenated hydrocarbons are preferably used.

【0045】

The reaction is smoothly carried out in the temperature range of -20°C to the
25 boiling point of the solvent used, and more preferably in the temperature range of -10°C to 150°C . The reaction is completed usually in several minutes to several ten hours.

After the reaction and a common post treatment, the targeted

2-oxabicyclo[3.3.0]octane compound (1) can be obtained by known separating means such as column chromatography, distillation, and the like.

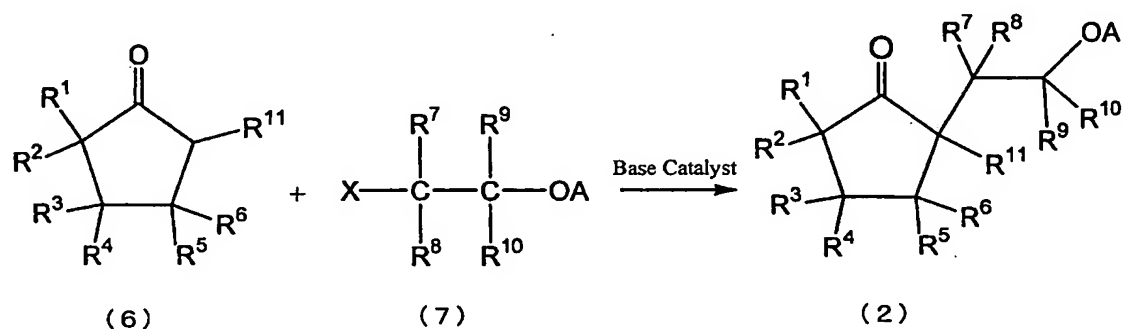
【0046】

The cyclopentanone compound (2) used as the raw material can be produced according to the method described in Tetrahedron Lett., 35, 7785 (1994), for example.

A common production route is shown as follows.

【0047】

【Chemical formula 12】



10 【0048】

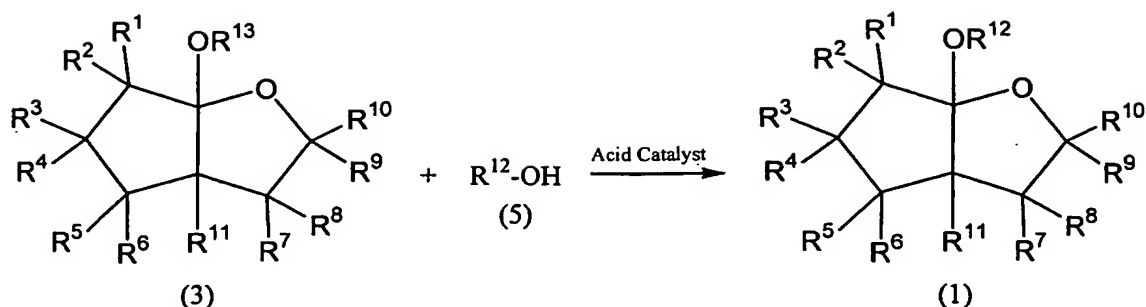
wherein R¹ to R¹¹ respectively represent the same groups as defined above and X represents a halogen atom. And A represents a hydrogen atom or a protective group of the hydroxyl group.

Specifically, the cyclopentanone compound (2) can be obtained by reacting a cyclopentanone compound of the formula (6) with a halogenated alkyl of the formula (7) in the presence of a base catalyst. As examples of the group A, an acetyl group, benzoyl group, tert-butyl group, 2-tetrahydropyranyl group, 2-tetrahydrofuranyl group, 1-ethoxyethoxy group can be given.

(ii) Process (2)

20 【0049】

【Chemical formula 15】



【0050】

The 2-oxabicyclo[3.3.0]octane compound (1) can be produced by reacting a compound of the formula (3) with an alcohol of the formula (5) in the presence of an acid catalyst.

【0051】

In the above formula, R^{13} represents a substituted or unsubstituted hydrocarbon group. As examples of the hydrocarbon group represented by R^{13} , alkyl groups such as a methyl group, ethyl group, n-propyl group, isopropyl group, and n-butyl group; alkenyl groups such as a vinyl group, 1-propenyl group, 2-propenyl group, 1-butenyl group, and 2-butenyl group; alkynyl groups such as an ethynyl group, 1-propynyl group, 2-propynyl group, 1-butylnyl group, and 2-butylnyl group; cycloalkyl groups such as a cyclopropyl group, cyclopentyl group, cyclohexyl group, and cyclooctyl group; cycloalkenyl groups such as a cyclopentenyl group, cyclohexenyl group, and cyclooctenyl group; and aryl groups such as a phenyl group, 1-naphthyl group, and 2-naphthyl group can be given.

【0052】

There are no specific limitations to the substituent for the hydrocarbon group represented by R^{13} , inasmuch as such a group is stable against acid catalysts. Examples include an alkoxy group, alkoxycarbonyl group, alkylthio group, alkylsulfonyl group, acyl group, acylamino group, nitro group, cyano group, halogen atom, substituted or unsubstituted phenyl group, and substituted or unsubstituted heterocyclic group.

【0053】

Of the above examples for R^{13} , due to easy removal of produced alcohols having the formula of $R^{13}OH$ from the reaction system, an alkyl group having 1-6 carbon atoms or an alkenyl group having 2-6 carbon-atoms is preferable, and an alkyl group having 1-3 carbon atoms is more preferable, with a methyl group being most preferable.

5 **【0054】**

As the acid catalyst, the same catalysts as those listed in the description of Process (1) can be given. The amount of the acid catalyst used is usually 0.0001-2 parts by weight, and preferably 0.001-1 part by weight, for 1 part by weight of the compound of the formula (3).

10 **【0055】**

The compound of the formula (3) can be produced by reacting a compound of the formula (2) with an alcohol of the formula $R^{13}OH$ in the presence of an acid catalyst. The same reaction conditions and the same type of acid catalyst as those mentioned in the description of Process (1) can be used.

15 **【0056】**

(3) Separating method of diastereomer mixture

In the third place, the present invention provides a method for separating a diastereomer mixture of 2-oxabicyclo [3.3.0]octane compound (1).

20 The separating method of the present invention is a method for separating a diastereomer mixture of 2-oxabicyclo [3.3.0]octane compound (1), in which (a) simulated moving bed chromatography or (b) a distilling method is used as a separation means.

【0057】

(a) Separating method using simulated moving bed chromatography

25 A simulated moving bed chromatographic separation apparatus is used for the simulated moving bed chromatography. In general, the separating apparatus has a packed bed consisting of several chambers (columns) packed with an adsorbent. The packed bed

has a structure to allow a liquid to circulate therein. The packed bed is provided with an eluant feed port, a first component (a strongly adsorbed component) drawing port, a sample feed port, and a second component (a weakly adsorbed component) drawing port in the direction of the liquid flow. The feed ports and drawing ports are caused to
5 intermittently move in the direction of the liquid flow. This operation has the same effect as that achieved by causing the adsorbing layer to move in the direction opposite to the liquid flow. Specifically, this type of apparatus can achieve a high separating performance with the same degree as that obtained by the moving bed chromatography in which separation is effected by causing the adsorbing layer to move. The strongly
10 adsorbed component refers to a diastereomer that can be adsorbed by the adsorbent more easily than the other diastereomer among at least two diastereomers and the weakly adsorbed component refers to the diastereomer which is adsorbed with a greater difficulty.

【0058】

15 Any known adsorbents that can separate the diastereomer mixture into individual streamers can be used as the adsorbent for the simulated moving bed chromatography without any specific limitation. As specific examples of the adsorbent, silica gel, neutral alumina, ion-exchange resin, zeolite, activated carbon, and synthetic adsorbent can be given. The type, average particle diameter, and the filling amount of the
20 adsorbent that can most efficiently separate the diastereomer mixture of the compound of the formula (1) into individual diastereomers can be appropriately selected.

【0059】

Fig. 1 is a schematic flow chart showing the liquid flow in a simulated moving bed chromatographic separation apparatus used in the present invention. In Fig. 1, 1
25 indicates an eluant feed port, 2 indicates a first component drawing port, 3 indicates a sample feed port, 4 indicates a second component drawing port, and 5 indicates a circulating liquid. 1a-4a individually indicate the positions of the feed ports and drawing

ports 1-4 in an operating period subsequent to a fixed-period operation.

【0060】

The liquid is circulated in the direction of a column a to a column h using a circulating pump (not shown). The eluant feed port 1, first component drawing port 2, sample feed port 3, and second component drawing port 4 are respectively provided in front of columns a, c, e, and g. In addition, the eluant feed port 1, first component drawing port 2, sample feed port 3, and second component drawing port 4 are respectively provided with a valve (not shown) which can be opened and closed. Opening and closing of the valves can be controlled as the whole separating apparatus.

10 As the valve, an electromagnetic type valve and the like can be given.

【0061】

After operation for a fixed period of time in this state, the eluant feed port 1, first component drawing port 2, sample feed port 3, and second component drawing port 4 are caused to move along the flow of the circulating liquid 5 to positions in front of the next column, whereby the eluant feed port 1, first component drawing port 2, sample feed port 3, and second component drawing port 4 are respectively shifted to the eluant feed port 1a, first component drawing port 2a, sample feed port 3a, and second component drawing port 4a. The apparatus is operated for a prescribed period of time (an operation switching time). This procedure is repeated.

20 【0062】

In order to efficiently separate a diastereomer mixture into individual diastereomers by operating the simulated moving bed chromatographic separation apparatus, the moving speed V1 ($V1 = \text{length of column} / \text{operation switching time}$) of the eluant feed port 1 and the like should be smaller than the moving speed V2 of the sample in the second component adsorbent, but larger than the moving speed V3 of the sample in the first component adsorbent ($V2 > V1 > V3$). Such operating conditions can be established by appropriately selecting the flow rate of liquid in each column, operation

switching time, and the type of eluant.

【0063】

By operating the simulated moving bed chromatographic separation apparatus in this manner, the packed bed can be apparently shifted in the direction reverse to the
5 flowing direction of the circulating liquid 5, whereby it is possible to continuously extract an eluate containing the first component and an eluate containing the second component respectively from the first component drawing port 2 and the second component drawing port 4.

【0064】

10 There are no specific limitations to the simulated moving bed chromatographic separation apparatus used in the present invention. The simulated moving bed chromatographic separation apparatuses described in Japanese Patent Applications Laid-open No. 3-168100 and No. 3-134562, for example, can be used.

【0065】

15 (b) Separating method using distilling method

A diastereomer mixture of 2-oxabicyclo[3.3.0]octane compound (1) can also be separated by distillation. Namely, it is possible to selectively collect one of the diastereomers from a solution containing a diastereomer mixture of 2-oxabicyclo[3.3.0]octane compound (1), by condensing the solution under reduced
20 pressure to remove unreacted materials, solvents, and the like optionally, and distilling the resulting residue.

【0066】

The distillation method is not specifically limited. For example, atmospheric distillation, reduced-pressure distillation, steam distillation, and the like can be used. Of
25 these, reduced-pressure distillation is preferable to increase the separating efficiency while suppressing thermal decomposition of 2-oxabicyclo[3.3.0]octane compound (1) to the minimum. There are no specific limitations to the distillation device. For example, a

known distillation device such as a rectification device comprising a rectification column packed with Sulzerpack can be used.

【0067】

5 The pressure and temperature of the reduced-pressure distillation are appropriately determined according to the type of the 2-oxabicyclo[3.3.0]octane compound to be separated. The pressure is usually 100-0.001 hPa, preferably 10-0.01 hPa, and more preferably 1-0.05 hPa. The distillation temperature indicated by oil bath temperature is usually 50-250°C, and preferably 70-200°C.

【0068】

10 In addition, selectivity of one diastereomer can be increased by increasing the reflux ratio during distillation. The reflux ratio indicates a ratio by weight of the amount of reflux to the amount of distillate (reflux/distillate) and is usually 30/1 or more, preferably 70/1 or more, and more preferably 600/1 or more, and still more preferably 1,200/1 or more.

15 **【0069】**

After selectively collecting only one diastereomer by distillation, the other diastereomers remain in the resulting still residue. The other diastereomers can be purified or isolated by a purification method such as distillation, column chromatography, crystallization, or the like.

20 **【0070】**

Although simulated moving bed chromatography or distillation are preferable methods of separating the diastereomer mixture into individual diastereomers in the present invention, other separating means such as silica gel column chromatography, for example, can be used.

25 **【0071】**

(4) Method of optically resolving alcohol

In the fourth place, the present invention provides a method of optically

resolving an optical isomer mixture of alcohol of the formula $R^{14}OH$, wherein R^{14} represents a substituted or unsubstituted hydrocarbon group having an asymmetric carbon atom.

【0072】

5 The optical resolution method of the present invention comprises a step of separating a diastereomer mixture of 2-oxabicyclo [3.3.0]octane compound (1) into individual diastereomers (Step A), a step of reacting the separated diastereomers with an alcohol of the formula $R^{13}OH$ in the presence of an acid catalyst to obtain 2-oxabicyclo[3.3.0]octane compound of the above formula (3) (Step B), a step of reacting
10 the 2-oxabicyclo[3.3.0]octane compound of the above formula (3) with an optical isomer mixture of alcohol of the formula $R^{14}OH$ in the presence of an acid catalyst to obtain a diastereomer mixture of 2-oxabicyclo[3.3.0]octane compound of the above formula (4) (Step C), a step of separating the resulting diastereomer mixture into individual diastereomers (Step D), and a step of reacting the separated diastereomers with an alcohol
15 of the formula $R^{15}OH$ in the presence of an acid catalyst to obtain optically active isomers of an alcohol of the formula $R^{14}OH$ (Step E).

【0073】

 This method of optically resolving alcohol will be described in more detail.
(Step A)

20 First, the diastereomer mixture of 2-oxabicyclo[3.3.0]octane compound (1) is separated into individual diastereomers. Although the above-described methods of using simulated moving bed chromatography, distillation, column chromatography, and the like can be used for the separation in this step, the method of using simulated moving bed chromatography or the distillation method are preferable.

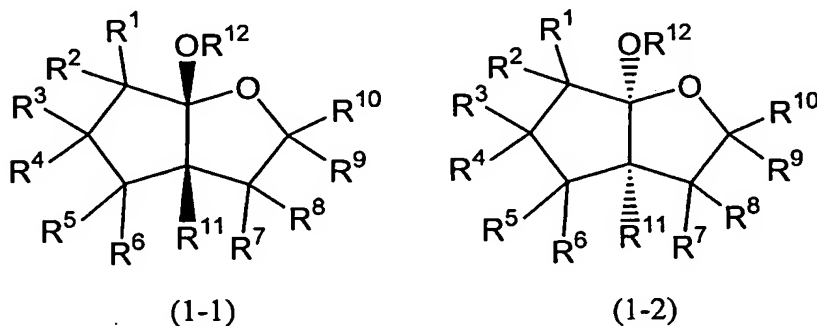
25 【00740】

 The separated diastereomers of the 2-oxabicyclo[3.3.0]octane compound (1) are compounds shown by the following formulas (1-1) or (1-2). These diastereomers are

optically active substances having a steric configuration, in which the position 1 substituent (R^{11}) and the position 5 substituent (OR^{12}) on the 2-oxabicyclo[3.3.0]octane ring are cis-configured with each other, with either substituent being on the α -plane (or β -plane) with respect to the other.

5 【0075】

 【Chemical formula 14】



 【0076】

 (Step B)

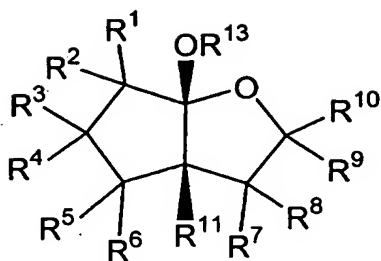
10 Next, the compound of the formula (1-1) or (1-2) is reacted with an alcohol of the formula $R^{13}OH$ in the presence of an acid catalyst to obtain the compound of the above formula (3). The compound of the above formula (3) is a compound shown by either the following formula (3-1) or (3-2). Since the reaction proceeds while

15 the compound of the formula (1-1) and the compound of the formula (3-2) is produced from the compound of the formula (1-2).

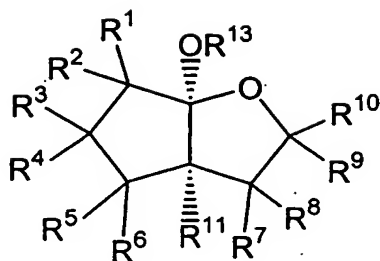
 The resulting compounds of the formula (3-1) or (3-2) can be used as an optical resolution agent of alcohol.

 【0077】

20 【Chemical formula 15】



(3-1)



(3-2)

【0078】

This step may be optionally omitted, in which case the compound of the above formula (1-1) or (1-2) can be used as an optical resolution agent as is.

5 (Step C)

【0079】

Next, the compound of the formula (3-1) or (3-2) is reacted with an optical isomer mixture of an alcohol of the formula $R^{14}OH$ in the presence of an acid catalyst to obtain a diastereomer mixture of the compound of the above formula (4). The same reaction conditions and acid catalysts as described in connection with Process 2 for the production of 2-oxabicyclo [3.3.0]octane compound (1) can be used.

【0080】

The alcohol represented by the formula $R^{14}OH$ is not limited inasmuch as the optical isomer mixture of an alcohol has an asymmetric carbon atom in the molecule. Any alcohol among primary alcohols, secondary alcohols, and tertiary alcohols can be used. As a specific example of the alcohol of the formula $R^{14}OH$, an optical isomer mixture of the same alcohol as the above alcohol (5) can be given.

【0081】

(Step D)

20 Next, the resulting diastereomer mixture of the formula (4) is separated into individual diastereomers. The separating method is not specifically limited. Separating methods such as common column chromatography, the above-described simulated

moving bed chromatography, the above-described distillation method, and crystallization can be given as examples. Of these, simulated moving bed chromatography and the distillation method are preferable.

【0082】

5 (Step E)

Next, the separated diastereomers are reacted with an alcohol of the formula, $R^{15}OH$, wherein R^{15} represents a substituted or unsubstituted hydrocarbon group, in the presence of an acid catalyst to obtain optically active isomers of an alcohol of the formula $R^{14}OH$. The resulting optical active alcohols can be isolated from the reaction solution by
10 a known purification-separation means such as distillation, column chromatography, and the like.

【0083】

In this instance, if the alcohol of the formula $R^{13}OH$ is used as an alcohol of the formula $R^{15}OH$, the compound of the above formula (3) can be regenerated by isolation
15 and can be reused as an optical resolution agent of alcohol.

【0084】

【Examples】

The present invention will now be described in detail by way of examples and comparative examples, which should not be construed as limiting the present invention.
20 It is possible to change kind of compound of the formula(1) , alcohol, reaction solvent and reaction temperature etc. within the present invention. In the examples and comparative examples below “parts” indicates “parts by weight”, unless otherwise specified.

【0085】

25 Preparation Example 1

Preparation of 2-(2-acetoxyethyl)-2-(2-propenyl)cyclopentanone

2-(2-Acetoxyethyl)-2-(2-propenyl) cyclopentanone (2-1) which is a starting raw

material was synthesized as described in Tetrahedron Lett., 35, 7785 (1994).

【0086】

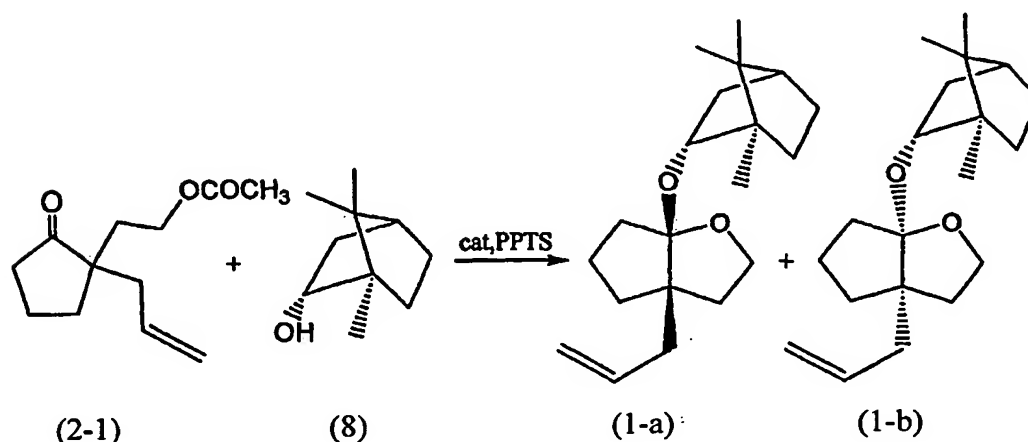
Example 1

Preparation of 1-(((1S)-endo)-(-)-bornyloxy)-5-(2-propenyl)-2-oxabicyclo[3.3.0]octane

5 [(1-a), (1-b)]

【0087】

【Chemical formula 16】



【0088】

16.9 parts of ((1S)-endo)-(-)-borneol (8) was added to a solution prepared by
10 adding 21.0 parts of 2-(2-acetoxyethyl)-2-(2-propenyl)cyclopentanone (2-1) and 2.5 parts
of pyridinium paratoluene sulfonate to 173 parts of toluene at room temperature. The
mixture was stirred for 10 hours at 110°C. The reaction mixture was filtered and the
filtrate was concentrated under reduced pressure. The resulting residue was purified by
silica gel column chromatography (n-hexane : diethyl ether = 40 : 1) to obtain 25.9 parts
15 of the target isomer mixture.

【0089】

The isomer mixture was developed by silica gel thin layer chromatography using
a 2:1 mixture of n-hexane and toluene as a developing solution to confirm that the R_f
values were 0.28 (Isomer 1) and 0.36 (Isomer 2) when developed for 44 mm.

【0090】

Example 2

Separation of diastereomer mixture using simulated moving bed chromatographic separation apparatus

- 5 A part of the isomer mixture obtained in Example 1 was fed to a simulated moving bed chromatographic separation apparatus having eight columns for semi-preparation with an inner diameter of 1 cm and a length of 10 cm packed with silica gel 60N spherical neutral particles (manufactured by Kanto Kagaku) at a flow rate of 0.03 ml/min (concentration: 25 vol%). Operating conditions of the simulated moving bed
10 chromatographic separation apparatus were as follows.

Eluant: 9 : 1 (by volume) mixture of n-hexane and ethyl acetate

Feed rate of eluant: 2.0 ml/min

Flow rate of strong adsorption component-rich fluid at the drawing port: 1.015 ml/min

- 15 Flow rate of weak adsorption component-rich fluid at the drawing port: 1.015 ml/min

Column switching time: 10 min

Temperature: room temperature

【0091】

- As a result of separating the above-mentioned isomer mixture after reaching a
20 stationary state under the above conditions, an optically active substance (Isomer 1) with an optical purity of 95% ee was obtained from the drawing port of strong adsorption component-rich fluid. On the other hand, an optically active substance (Isomer 2) with an optical purity of 97% ee was obtained from the drawing port of weak adsorption component-rich fluid. Productivity is shown in Table 1. Productivity is evaluated by the
25 amount of the compound isolated per hour (g/hr).

【0092】

The properties of the diastereomers are shown as follows.

<Properties of Isomer 1>

EI-MS: m/z 304 (M^+)

FT-IR (nujor): 3180, 2960, 2880, 1645, 1478, 1460, 1395, 1375, 1325, 1310, 1240, 1195, 1120, 1058, 1025, 960, 948, 920 cm^{-1}

5 $^1\text{H-NMR}$ (CDCl_3 , δ ppm): 0.80 (s, 3H), 0.84 (s, 6H), 0.95-2.22 (m, 16H), 2.27 (m, 1H), 3.70-3.92 (m, 3H), 5.04-5.09 (m, 2H), 5.88 (ddd, $J = 7.0, 10.0, 16.5\text{Hz}$, 1H),

Optical rotation: $[\alpha]_D^{25} = +5.56^\circ$ ($c = 0.84$, CHCl_3)

【0093】

10 <Properties of Isomer 2>

EI-MS: m/z 304 (M^+)

FT-IR (nujor): 3180, 2960, 2880, 1645, 1480, 1460, 1400, 1375, 1330, 1310, 1240, 1195, 1125, 1060, 1025, 960, 948, 920 cm^{-1}

15 $^1\text{H-NMR}$ (CDCl_3 , δ ppm): 0.80 (s, 3H), 0.84 (s, 6H), 0.95-2.22 (m, 16H), 2.27 (m, 1H), 3.98-4.10 (m, 1H), 3.70-3.92 (m, 2H), 5.04-5.09 (m, 2H), 5.88 (ddd, $J = 7.0, 10.0, 16.5\text{Hz}$, 1H),

Optical rotation: $[\alpha]_D^{25} = -74.18^\circ$ ($c = 1.05$, CHCl_3)

【0094】

Comparative Example 1

20 Separation of diastereomer mixture using high performance liquid chromatographic separation apparatus

A part of the isomer mixture obtained in Example 1 was fed to a high performance liquid chromatographic separation apparatus having eight columns for semi-preparation with an inner diameter of 1 cm and a length of 10 cm packed with silica gel 60N spherical neutral particles (manufactured by Kanto Kagaku). An eluate was collected at the outlet port using a fraction collector. Operating conditions of the high performance liquid chromatographic separation apparatus were as follows.

25

Eluant: 2 : 1 (by volume) mixture of n-hexane and toluene

Flow rate: 2.0 ml/min.

Fraction switching time: 5 min

5 **【0095】**

 An optically active substance with an optical purity of 93% ee was obtained from the drawing port of weak adsorption component-rich fluid of fractions No. 1 to No. 4. An optically active substance with an optical purity of 90% ee was obtained from the drawing port of strong adsorption component-rich fluid of fractions No. 36 to No. 39. Fractions
10 from No. 5 to No. 35 were obtained as mixtures of weak adsorption components and strong adsorption components, which could not be separated. The total period of time required for the processing was 5.2 hours. Productivity is shown in Table 1.

【0096】

【Table 1】

15 Table 1

	Example 1	Comparative Example 1
Isomer 1 (g/h)	0.20	0.002
Isomer 2 (g/h)	0.25	0.013

【0097】

 The results of Table 1 confirm that the simulated moving bed chromatographic separation apparatus can separate a diastereomer mixture into individual diastereomers continuously and more efficiently as compared with a conventional high performance
20 liquid chromatographic separation apparatus.

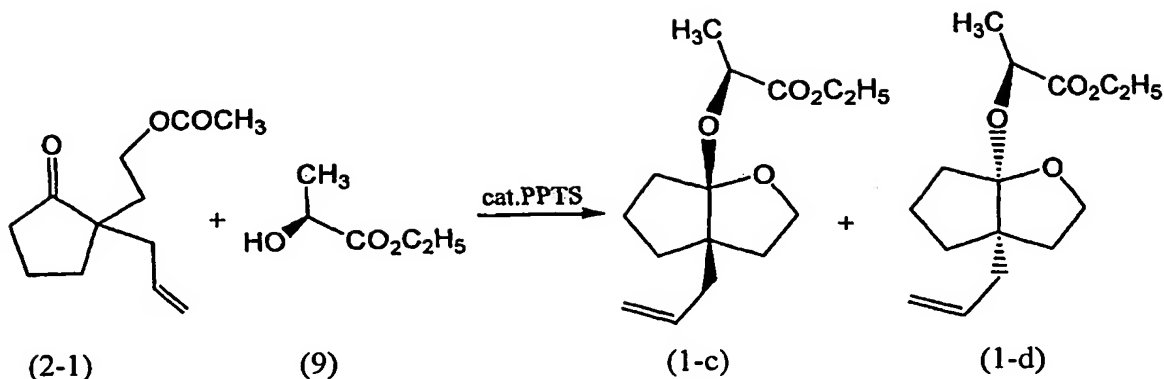
【0098】

Example 3

Preparation of 1-((1S)-ethoxycarbonylethoxy)-5-(2-propenyl)-2-oxabicyclo[3.3.0]octane
[(1-c), (1-d)]

【0099】

【Chemical formula 17】



【0100】

A solution prepared by adding 42.0 parts of

- 5 2-(2-acetoxyethyl)-2-(2-propenyl)cyclopentanone (2-1) to 136 parts of methylene chloride was added dropwise to a solution of 5 parts of pyridinium paratoluene sulfonate (PPTS) and 26.0 parts of (S)-(-)-ethyl lactate (9) in 200 parts of methylene chloride at 0°C. The mixture was stirred at room temperature for 30 minutes. The reaction solution was washed with saturated brine, dried over anhydrous sodium sulfate, and filtered. The
- 10 resulting residue obtained by concentrating the filtrate under reduced pressure was purified by silica gel column chromatography using an eluant (n-hexane : diethyl ether = 20 : 1) in an amount of 50 times by weight of the residue to obtain 46.6 parts of a mixture of isomers.

【0101】

- 15 The isomer mixture was developed by silica gel thin layer chromatography using a 4:1 mixture of n-hexane and diisopropyl ether as a developing solution to confirm that the R_f values were 0.32 (Isomer 3) and 0.41 (Isomer 4) when developed for 69 mm.

【0102】

As a result of separating the above-mentioned isomer mixture using the same

simulated moving bed chromatographic separation apparatus as that used in Example 2 after reaching a stationary state under the same conditions as in Example 2, an optically active substance (Isomer 3) with an optical purity of 96% ee was obtained from the drawing port of strong adsorption component-rich fluid. On the other hand, an optically active substance (Isomer 4) with an optical purity of 98% ee was obtained from the drawing port of weak adsorption component-rich fluid.

【0103】

The properties of the resulting isomers are as follows.

10 <Properties of Isomer 3>

EI-MS: m/z 268 (M^+)

FT-IR (Nujor); 3060, 2980, 2950, 2930, 2870, 1755, 1738, 1640, 1450, 1375, 1300, 1270, 1185, 1140, 1130, 1120, 950, 915 cm^{-1}

15 $^1\text{H-NMR}$ (CDCl_3 , δ ppm); 1.27-1.71 (m, 12H), 2.00 (m, 1H), 2.01-2.16 (m, 2H), 2.17-2.39 (m, 1H), 3.75-3.79 (m, 2H), 4.14-4.20 (m, 3H), 5.03-5.10 (m, 2H), 5.90 (ddd, 1H),

Optical rotation: $[\alpha]_D^{25} = -0.10^\circ$ ($c = 5.50$, CHCl_3)

【0104】

<Properties of Isomer 4>

20 EI-MS: m/z 268 (M^+)

FT-IR (Nujor); 3065, 2970, 2960, 2880, 1755, 1740, 1645, 1455, 1365, 1310, 1275, 1190, 1125, 1045, 915 cm^{-1}

$^1\text{H-NMR}$ (CDCl_3 , δ ppm); 1.26-1.75 (m, 12H), 1.93-1.96 (m, 2H), 2.21-2.28 (m, 2H), 3.78-3.86 (m, 2H), 4.15-4.20 (m, 2H), 4.37-4.38 (m, 1H), 5.02-5.09 (m, 2H), 5.91 (ddd, 1H)

25 Optical rotation: $[\alpha]_D^{25} = -74.75^\circ$ ($c = 8.85$, CHCl_3)

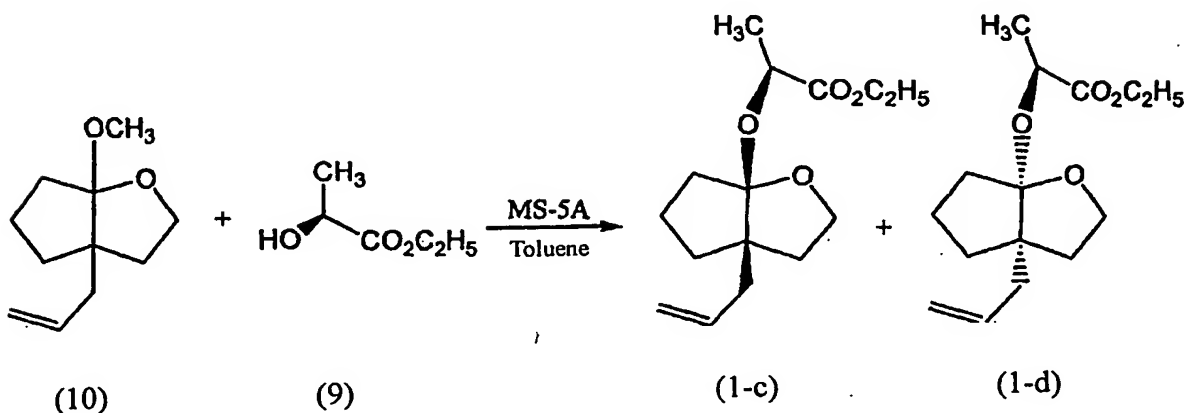
【0105】

Example 4

Preparation of 5-(2-propenyl)-1-((1S)-ethoxycarbonylethoxy)-2-oxabicyclo[3.3.0]octane [(1-c), (1-d)]

【0106】

5 【Chemical formula 18】



【0107】

10 10.6 parts (S)-(-)-ethyl lactate (9) and 18.2 parts of molecular sieve (MS-5A) were added to 184 parts of anhydrous toluene. After the addition of 18.2 parts of 1-methoxy-5-(2-propenyl)-2-oxabicyclo[3.3.0]octane at room temperature, the resulting mixture was refluxed for seven hours. In this instance, 364 parts of molecular sieve (MS-4A) that can adsorb methanol was filled in the reflux tube to adsorb the methanol in the reflux tube. After the reaction, the reaction solution was filtrated. The filtrate was concentrated under reduced pressure and the resulting residue was distilled under reduced pressure using a 9-plate mini-throughther (manufactured by Tokaseiki Co., Ltd.). The
15 unreacted compound (9) was first collected. Then, the diastereomer mixture was separated by distillation. The distillation conditions were as follows.

【0108】

<Conditions for collecting unreacted compound (10)>

Oil bath temperature: 140°C

Still temperature: 110°C

Column top temperature: 50.4°C/1.0 mmHg

Reflux ratio: (Reflux amount)/(Distillate amount) = 10/1 (by weight)

【0109】

5 <Isomer mixture separating conditions>

Oil bath temperature: 164°C

Still temperature: 132°C

Column top temperature: 104.6°C/1.0 mmHg

Reflux ratio: (reflux amount)/(distillate amount) was changed in the order of

10 30/1 → 70/1 → 600/1 → 1200/1

The distilled product was a mixture of the Isomer 3 and Isomer 4.

The results of analysis by gas chromatography of distillate components when the ratio (reflux amount : distillate amount) was 1:30, 1: 70, 1:600, or 1:1200 is shown in

15 Table 2.

【0110】

【Table 2】

Table 2

	Reflux ratio 1:30	Reflux ratio 1:70	Reflux ratio 1:600	Reflux ratio 1:1200
Isomer 3	40	35	25	5
Isomer 4	60	65	75	95

【0111】

20 The results of Table 2 confirmed that if a diastereomer mixture (a mixture of Isomer 3 and Isomer 4) respectively represented by the formulas (1-c) and (1-d) is distilled under reduced pressure, one of the diastereomers (Isomer 4 in this Example) can be selectively isolated. It was further confirmed that the higher the reflux ratio, the higher the selectivity of isolation of Isomer 4 by distillation.

【0112】

Example 5

Optical resolution of 2-octanol (optical isomer mixture)

5 (1) Preparation of optically active 1-methoxy-5-(2-propenyl)-2-oxabicyclo[3.3.0]octane

300 parts of one of the diastereomers of

1-(((1S)-endo)-(-)-bornyloxy]-5-(2-propenyl)-2-oxabicyclo[3.3.0]octane (isomer having a larger RF) obtained in Example 2 was dissolved in 3,000 parts of anhydrous methanol, and 30 parts of PPTS was added. The mixture was refluxed for 12 hours. After cooling to
10 room temperature, 60 parts of potassium carbonate was added to the reaction solution and the mixture was stirred for 15 minutes. The reaction solution was poured into water. The mixture was extracted with diethyl ether three times. The organic layer was combined, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under reduced pressure and the resulting residue was purified by silica gel column
15 chromatography (n-hexane : ethyl acetate = 10 : 1) to obtain 166 parts of a target product. The yield was 92%.

【0113】

(2) Preparation of diastereomer mixture of

1-(2-octyloxy)-5-(2-propenyl)-2-oxabicyclo[3.3.0]octane

20 A reaction vessel was charged with 870 parts of anhydrous toluene, 54 parts of an optical isomer mixture of 2-octanol, 80 parts of molecular sieve (MS-5A), and 80 parts of 1-methoxy-5-(2-propenyl)-2-oxabicyclo[3.3.0]octane obtained in (1) above at room temperature. The mixture was refluxed for five hours with stirring. In this instance, the reaction vessel was equipped with a reflux tube packed with 160 parts of molecular-sieve
25 (MS-4A) that can adsorb methanol to adsorb the methanol generated in the reaction system. After the reaction, the reaction solution was filtered and the filtrate was concentrated under reduced pressure to obtain 117 parts of the target diastereomer

mixture of 1-(2-octyloxy)-5-(2-propenyl)-2-oxabicyclo[3.3.0]octane. The yield was 95%.

The diastereomer mixture was identified by measurement of the FT-IR, ¹H-NMR spectrum, and ¹³C-NMR spectrum.

5 **【0114】**

(3) Separation of diastereomer mixture of

1-(2-octyloxy)-5-(2-propenyl)-2-oxabicyclo[3.3.0]octane

110 parts of the diastereomer mixture of
1-(2-octyloxy)-5-(2-propenyl)-2-oxabicyclo[3.3.0]octane prepared in (2) above was
10 separated into individual diastereomers using the same technique of simulated moving
bed chromatography as that used in Example 2.

As a result of separating the isomer mixture after reaching a stationary state, an
optically active substance (Isomer 5) with an optical purity of 96% ee was obtained from
the drawing port of strong adsorption component-rich fluid. On the other hand, an
15 optically active substance (Isomer 6) with an optical purity of 98% ee was obtained from
the drawing port of weak adsorption component-rich fluid. The productivity was 0.5 g/h
in the case of Isomer 5 and 0.45 g/h in the case of Isomer 6.

【0115】

(4) Isolation of optically active 2-octanol

20 175 parts of one diastereomer (Isomer 5) was dissolved in 4,000 parts of
anhydrous methanol and 16 parts of pyridinium p-toluenesulfonate (PPTS) was added.
Then, the mixture was refluxed for 12 hours. After cooling to room temperature, 20 parts
of potassium carbonate was added to the reaction solution and the mixture was stirred for
15 minutes. The reaction solution was poured into water. The mixture was extracted with
25 diethyl ether three times. The organic layer was combined, dried over anhydrous sodium
sulfate, and filtered. The filtrate was concentrated under reduced pressure. The resulting
residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 10 :

1) to obtain 95 parts (yield 94%) of the target optically active 2-octanol and 108 parts (yield 96%) of 1-methoxy-5-(2-propenyl)-2-oxabicyclo[3.3.0]octane.

【0116】

The same procedure as above was carried out for another diastereomer (Isomer 6) with to obtain the other optically active 2-octanol (yield 94%). At the same time, 1-methoxy-5-(2-propenyl)-2-oxabicyclo[3.3.0]octane was collected (yield 95%).

【0117】

The optical rotation of the resulting optically active 2-octanols were as follows.

(S)-(+)-2-octanol $[\alpha]^{25}_D = +10.0^\circ$ (c = 1, C₂H₅OH)

10 (R)-(-)-2-octanol $[\alpha]^{25}_D = -10.0^\circ$ (c = 1, C₂H₅OH)

The optical rotation of the resulting optically active 2-octanols showed good agreement with the known data, indicating that optical resolution was successful.

【0118】

【Effect of the invention】

15 According to the present invention, an optical resolution agent (a 2-oxabicyclo[3.3.0]octane compound) which can optically resolve an alcohol having an asymmetric carbon atom in the molecule in a simple manner can be provided.

According to the present invention, the compound of the present invention can be produced in a high yield by a short path.

20 According to the method for separating a diastereomer mixture using the simulated moving bed chromatography of the present invention, an optically active substance (diastereomer) with a high optical purity can be obtained efficiently and continuously. Since a wide variety of solvents can be used as an eluant, the method has excellent generality and versatility. According to the method for separating a
25 diastereomer mixture by distillation of the present invention, an optically active substance (diastereomer) with a high optical purity can be obtained efficiently and continuously.

【BRIEF DESCRIPTION OF THE DRAWINGS】

【Fig.1】

Fig. 1 is a flow chart showing a flow of fluid in a simulated moving bed chromatographic separation apparatus used in the present invention.

5 【Explanations of letters or numerals】

a,b,c,d,e,f,g,h...column packed with an adsorbent

1...an eluant feed port

1a...an eluant feed port after operation for a fixed period of time

2...a first component drawing port

10 2a...a first component drawing port after operation for a fixed period of time

3... a sample feed port

3a... a sample feed port after operation for a fixed period of time

4...a second component drawing port

4a...a second component drawing port after operation for a fixed period of time

15 5...circulating liquid

【Name of Document】 ABSTRACT

【Abstract】

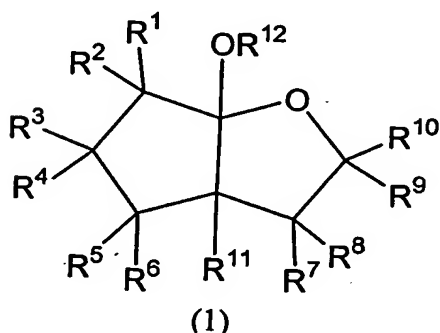
【Object】

To provide a novel 2-oxabicyclo[3.3.0]octane compound (hereinafter referred to
5 as compound (1)) which can be used as an optical resolving agent of an optical isomer
mixture such as alcohol, a process for producing the same, a method of separating a
diastereomer mixture of the compound, and a method of optically resolving alcohol.

【Means for Settlement】

Compound (1) as shown below, a process for producing the same, a method of
10 separating a diastereomer mixture of a compound (1) by simulated moving bed
chromatography or distillation to separate into individual diastereomers, method of
optically resolving alcohol using the separated diastereomer.

【Chemical formula 1】



15 [In the formulae, R¹-R¹⁰ individually represent a hydrogen atom etc., R¹¹ represents a
2-propenyl group etc., and R¹² represents a substituted or unsubstituted chiralic
hydrocarbon group]

【Chosen Drawing】 None

【Name of Document】 DRAWING

【Fig.1】

